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Critical Review

Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee

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Pencil-beam scanning (PBS) proton therapy (PT), particularly intensity modulated PT, represents the latest advanced PT technology for treating cancers, including thoracic malignancies. On the basis of virtual clinical studies, PBS-PT appears to have great potential in its ability to tightly tailor the dose to the target while sparing critical structures, thereby reducing treatment-related toxicities, particularly for tumors in areas with complicated anatomy. However, implementing PBS-PT for moving targets has several additional technical challenges compared with intensity modulated photon radiation therapy or passive scattering PT. Four-dimensional computed tomography–based motion management and robust

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optimization and evaluation are crucial for minimizing uncertainties associated with beam range and organ motion. Rigorous quality assurance is required to validate dose delivery both before and during the course of treatment. Active motion management (eg, breath hold), beam gating, rescanning, tracking, or adaptive planning may be needed for cases involving significant motion or changes in motion or anatomy over the course of treatment.

Introduction

Proton therapy (PT) for thoracic cancers can often spare more nearby critical structures than intensity modulated photon radiation therapy (IMRT) (1-6). Passive scattering proton therapy (PSPT) technology, however, relies on 3-dimensional (3D) conformal treatment planning, with its inherent limitations resulting from the lack of intensity modulation (7).

Tumors in complex anatomic positions and tumors that curve around critical structures are extremely challenging to treat with PSPT because of the inability of PSPT to adjust its modulation width for the various thicknesses throughout a target. This can lead to difficulty in minimizing the mean lung dose, the lung volume received 20 Gy and above, and especially, the mean esophageal dose. In such cases, dose coverage may be intentionally compromised to avoid damaging critical normal tissue structures.

In contrast to PSPT, pencil-beam scanning (PBS) PT, especially intensity modulated proton therapy (IMPT)—one of several pencil-beam delivery optimization strategies—can simultaneously optimize the intensities of pencil beams by using an objective function that accounts for the shape and density of targets, as well as constraints on normal tissues. Dosimetric studies have demonstrated that PBS-PT, especially IMPT, can reduce the dose to critical normal tissues relative to IMRT and allow individualized radical radiation therapy for clinically challenging cases of stage III non−small cell lung cancer (NSCLC) (8-10). However, uncertainties regarding the range of the proton beam going through heterogeneous tissues, the interplay effect between the motion of the scanning beam and respiratory motion, and other aspects of treatment planning and quality assurance are more challenging and complex for PBS-PT, especially IMPT, than for PSPT or IMRT (11-15).

Preliminary results have shown that PBS-PT technology can be safely implemented in the treatment of thoracic cancers with minimal motion, and clinical outcomes seem promising (16, 17). As additional proton centers, many exclusively with PBS technology, are being built around the world, the need for guidelines and consensus to address these issues associated with PBS-PT is increasingly desirable. To meet this need, the Particle Therapy Co-Operative Group (PTCOG) Thoracic and Lymphoma Subcommittee developed this consensus guideline, on the basis of available physics and clinical findings, for the use of PBS-PT including IMPT for thoracic tumors.

Major Challenges of PBS-PT in Thoracic Cancers

Dosimetric impact of range uncertainty and respiratory motion

In PT, unlike in photon therapy, the range uncertainty resulting from the uncertainty in the Hounsfield units (HUs) of computed tomography (CT) images and the values of stopping powers must be accounted for. The range uncertainty has the potential to alter the proton range and dose distribution, which can result in underdosing the target volume or overdosing critical structures. Additional uncertainties from setup errors and intrafractional organ motion (primarily from respiration) not only cause geometric displacement of tumors and normal tissues, blurring the dose gradient from target volume to normal tissue, but also can affect tissue densities, which can alter the ranges of protons and influence dose distribution. An additional source of uncertainty comes from interfractional organ motion brought about by the opening of previously blocked airways and anatomic changes (eg, the accumulation or drainage of fluid), which can significantly change the proton range along the path of the proton beam.

The influence of these uncertainties becomes more significant in IMPT or multifield-optimized (MFO) plans (defined in Appendix E1; available online at www.redjournal.org) because the individual fields can be highly modulated and steep dose gradients can be located in the middle of the target (18). Hence, the concept of a "safety margin" is less effective for ensuring coverage with PBS-PT.

In addition, when PBS technology is used to treat moving tumors, the interplay effect results in misplacement of the individual pencil-beam spots relative to the planned positions and can cause additional degradation of the delivered dose distribution, potentially manifesting as extreme local tumor underdosage or normal structure overdosage (11, 12, 15, 19, 20). This effect is most pronounced when PBS-PT is delivered in a limited number of fractions such as in stereotactic ablative radiation therapy (21), which can involve $\leq$5 fractions.

Dosimetric impact of heterogeneity of chest

In addition to motion uncertainty, tissue density heterogeneity of chest organs can have a significant impact on

proton dose distribution. Proton dose tends to extend a greater physical distance in low-density tissues. The density of lung parenchyma is only about one-third of that of solid tissues such as the heart and major vessels. In addition, the trachea and bronchus have airways. These unique complexities of the chest organs can impose significant challenges for predicting accurate PBS-PT dose distribution especially under the influence of organ or target motion. In addition, dose calculation accuracy in heterogeneous tissues may be a concern (11).

Basic Requirements for Implementing PBS-PT in Thoracic Cancers

To understand basic dosimetric properties under the influence of moving organs and targets, each institution should perform basic measurements using a moving phantom that can be as simple as slabs on the 1-dimensional moving platform. Through measurements under different delivery conditions, including but not limited to different target sizes and locations, as well as the number of repainting of the target, it is possible to establish a threshold of the motion amplitude in which the interplay effect is small for various scenarios. For example, Tsunashima (22) demonstrated that the interplay effect was minimal for a motion amplitude <5 mm for a particular set of beam properties. For thoracic cancers treated with PBS, 4-dimensional (4D) CT−based motion evaluation, management, planning, and delivery is required as described in the following sections.

Treatment Simulation, Contouring, and Target Definition

All patients should undergo 4D CT−based treatment simulation to determine the magnitude of tumor motion (23). For patients who can be treated while "free breathing," an internal gross tumor volume (IGTV) should be generated by using either a union of gross tumor volumes (GTVs) on all respiratory phases or an outline of GTV on the maximum intensity projection CT scan and verified through different breathing phases. For patients to be treated with breath hold (BH), multiple BH CT scans should be acquired and the IGTV should be generated by using a union of all GTVs defined on each different BH scan. For patients to be treated with respiratory gating, the IGTV should be defined based on the gating window. The internal clinical target volume (ICTV) is defined as a 5- to 10-mm (or more for esophageal cancer) isotropic expansion of the IGTV that is edited clinically based on the pattern of tumor spread and anatomic boundaries (vertebral body, chest wall, esophagus, heart, and great vessels, among others). It should be pointed out that the ICTV defined here is somewhat different from the internal target volume defined by the International Commission on Radiation Units & Measurements (24). The planning target volume (PTV), defined as an expansion of the ICTV, typically by 5 mm, should be used for reporting and evaluation purposes (25). Strictly speaking, the PTV concept cannot be directly used for PT planning because the range uncertainties are beam direction specific. Beam-specific PTVs (26, 27) or water-equivalent thickness (WET)−internal target volume (28) could be used for single-field optimized (SFO) plans (defined in Appendix E1; available online at www.redjournal.org).

Treatment Planning

For free-breathing treatment, the averaged 4D CT set with an IGTV density override (ie, using an average HU inside the solid GTV [typically 40-60 HU]) (29) should be used to create PBS plans. Two "verification" dose distributions, created by recalculating the dose on the 4D CT scans at 2 extreme breathing phases (maximum inhale [T0] and maximum exhale [T50]) with the original plan, should be generated, and the original plan should be adjusted until the verification and original dose distributions all meet the required target coverage and normal tissue criteria. Similarly, plans for patients undergoing BH and plans for patients undergoing gating should be developed on 1 BH scan and 1 phase CT scan within the gating window, respectively, if target motion is greater than each institutionally established threshold value and validated on additional BH CT scans (for BH patients) or phase CT scans (for gating patients).

In general, if there is significant motion (eg, >5-10 mm), an SFO technique is preferred to minimize motion uncertainty particularly when 4D dose calculation and/or evaluation and robust optimization tools are not available. An SFO plan with multiple fields is effectively equivalent to multiple volumetric rescannings (30). An MFO technique should be used to treat patients with little target motion or patients for whom proper motion mitigation strategies are successfully applied. MFO plans usually produce more conformal dose distributions than SFO plans; however, they are more sensitive to target motion or variation of the radiologic path length from each beam.

Motion Management Strategies

Personalized (patient-specific) motion analysis

The motion of thoracic tumors has been evaluated on 4D CT images (31-34). Thoracic tumors do move, but most have limited motion. For example, for locally advanced NSCLC, only 35% to 39% of tumors move >0.5 cm and only 5% of tumors move >1.3 cm in the superior-inferior direction; on the other hand, among early-stage tumors, about 50% move >0.5 cm and 5% move >2.0 cm in the superior-inferior direction (31, 34). In a study involving real-time measurement of implanted fiducial markers with orthogonal fluoroscopic imaging, Seppenwoolde et al (35)

found that tumor motion owing to respiration was greatest in the superior-inferior direction, especially for unfixed tumors in the lower lobe of the lung. In studies of tumor motion for photon therapy, motion was normally characterized in terms of the centroid movement of the GTV (31, 32, 35, 36). For PT, one needs to know not only the centroid movement but also changes in tissue density along the entire proton beam path owing to respiration (usually measured with the WET method, as described later). For PBS-PT, the dosimetric impact of tumor motion is an even more complex function involving intrafractional and interfractional motion, the size of the target volume, the treatment plan, and the delivery system, including the scanning time, spot size, number of fields used, and number of fractions, among other factors (15, 18-20).

Potential effects of intrafractional motion from respiration on the treatment plan should be assessed by analyzing the motion in directions both parallel and perpendicular to the beam axis. The maximum inhale (T0) and maximum exhale (T50) phases of 4D CT simulation images should be mapped by using deformable image registration software (37, 38). The deformation vectors of voxels contained in the target volume should be used to calculate the distance traveled by the tissue in the direction that is both perpendicular ($M\perp$) and parallel ($M\|$) to the beam axis, as described in detail in Appendix E2 (available online at www.redjournal.org).

The analysis and recommendations described in Appendix E2 (available online at www.redjournal.org) are consistent with previous recommendations (30) to select beam directions as parallel as possible to the main direction of target motion. However, the greatest motion is often along the superior-inferior direction (31, 34, 35), which is not feasible for beam direction selection.

Consideration of proton beam path length, previous irradiation (if applicable), patient anatomy, and the WET and motion analyses should be used to select beam angles for a given patient by use of an iterative process, while one should keep in mind that the beam should not range into the critical structures, especially those that could be affected by motion interplay or anatomic changes. For patients previously treated with radiation therapy, consideration should be given to choosing beam angles in which the dose passes through the nonfunctional or fibrotic lung and limits the dose to previously irradiated portions of the esophagus, spinal cord, brachial plexus, heart, and skin to minimize the risk of severe side effects.

Motion analysis tools such as the tool described here are not currently commercially available. We strongly encourage vendors of treatment planning systems to implement similar tools as an integral part of these systems (39, 40).

Four-dimensional dose and dynamic dose

The motion analysis described earlier is the first step toward personalized motion management. It does not provide any quantitative information on the dosimetric impact of motion. For example, for the same magnitude of motion, the dosimetric effect is much larger for a smaller target volume than for a larger volume because of interplay effects (19, 20). The concepts of 4D accumulated dose (4DD) and 4D dynamic accumulated dose (4DDD) based on 4D CT images should be used to estimate the dosimetric impact. Unfortunately, 4DD and 4DDD are not available for most commercial planning systems. Vendors of treatment planning systems are strongly encouraged to implement 4DD and 4DDD as an integral part of their systems.

The 4DD is the averaged sum of the doses calculated on all N (typically 10) individual phases of a 4D CT scan using the planned fluence without considering the time dependence of the delivery fluence. To calculate the 4DDD, details on the time dependence of the delivery fluence are considered together with changes in anatomy owing to respiratory motion (19, 20, 41). A detailed discussion of 4DD and 4DDD is presented in Appendix E3 (available online at www.redjournal.org). Assuming that the 4D CT scan is a true representation of the patient's anatomy, studies have shown that the 4DDD converges to the 4DD, meaning that the interplay effect can be averaged out because of its random nature, after multiple fractions (41, 42). The recalculated dose distributions on T0 and T50 represent the extremes of systematic differences from the nominal dose distribution (41, 43) and can be used to quantify the dose degradation owing to respiratory motion.

One group has proposed using the difference between single-fraction 4DD (1FX4DD) and single-fraction 4DDD (1FX4DDD) to evaluate interplay effects on treatment plans (20, 43). Figure 1 is an example of a clinical workflow based on using the difference between 1FX4DD and 1FX4DDD to evaluate the coverage of the target volume by the prescribed dose. If the difference is less than the established criterion (in this example, 3%), the patient could be treated with PBS-PT. If the criterion cannot be met, several techniques to effectively reduce the interplay effect could be used during the planning process, including selecting the scanning direction along the largest component of motion (22, 44-46), smaller spot spacing (47), optimized delivery sequence (48), layered rescanning (20, 49, 50), or volumetric rescanning (27, 30, 49-51). Notably, reducing spot spacing will increase treatment delivery time as well as increase the possibility of a monitor unit (MU) "starvation" effect due to minimum MU per spot (52). If the interplay effect must be reduced further, another option is to use (*1*) 3D robust optimization (53) or 4D robust optimization (43, 53); or (*2*) motion mitigation strategies, if available, during treatment delivery, including rescanning (either layered rescanning [20, 49, 50] or volumetric rescanning [30, 49-51]), BH (54), gating (55, 56), and tracking (57, 58). All of these strategies in the planning and delivery processes could be used independently or in combination for individual patients, but the selection is subject to which strategies are available at the treating institution. In any event, if the dosimetric criteria are met, the patient can be treated with PBS-PT; otherwise, PBS-PT should not be offered.

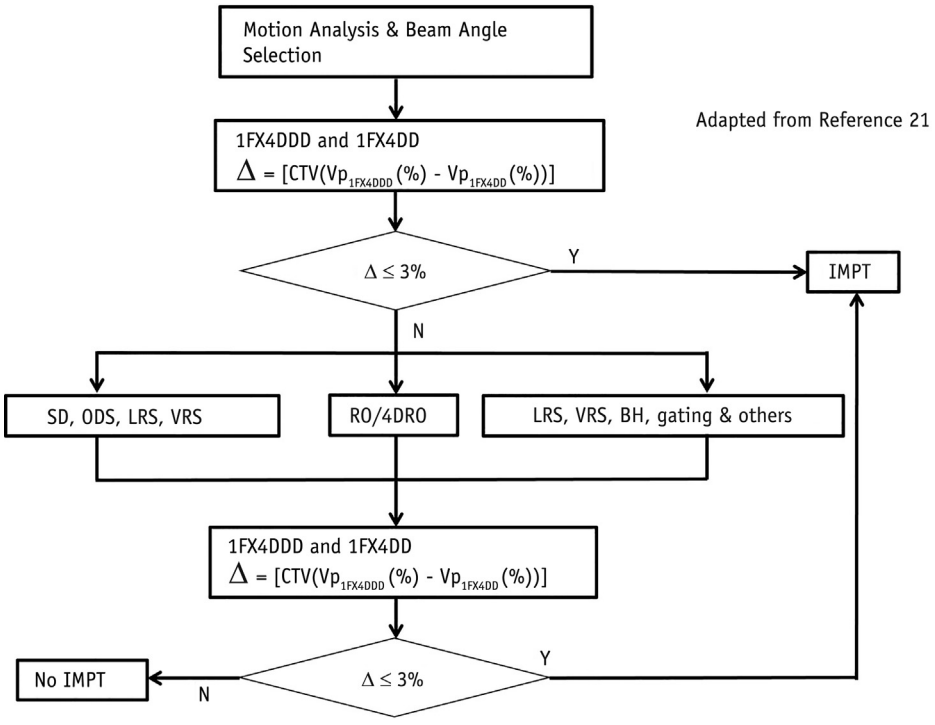

Fig. 1. Example of a clinical workflow based on using the difference between single-fraction 4-dimensional dynamic accumulated dose (1FX4DDD) and single-fraction 4-dimensional accumulated dose (1FX4DD) to evaluate the target volume to be covered by the prescribed dose, with various motion mitigation strategies to be used if needed. *Abbreviations:* BH = breath hold; CTV = clinical target volume; 4DRO = 4-dimensional robust optimization; IMPT = intensity modulated proton therapy; LRS = layered rescanning; N = no; ODS = optimized delivery sequence; RO = robust optimization; SD = scanning direction; Vp = volume of CTV that receives at least prescribed dose; VRS = volumetric rescanning; Y = yes.

Robust evaluation and 3D and 4D robust optimization

A robust evaluation method for PBS-PT based on worst-case scenarios was first introduced by Lomax (11). This worst-case robustness approach (Appendix E4; available online at www.redjournal.org, for some details) has also been implemented for 3D robust optimization (13, 59, 60). A difference of less than some threshold value (most commonly, 5%) between the worst-case dose distribution and the nominal dose is considered acceptable. If the plan is not robust (ie, it exceeds the threshold value), then the plan should be reoptimized. Inoue et al (38) recently demonstrated that 3D robustly optimized plans for stage III NSCLC are only minimally affected by setup and range uncertainties, breathing motion, and interplay effects.

The 3D robust optimization technique has been extended to 4D robust optimization by incorporating the 4D CT images from all breathing phases (43, 53, 61). In practice, it may be sufficient to only include the maximum inhale (T0) and maximum exhale (T50) of the 4D CT images in addition to the planning CT dataset of the averaged 4D CT images (43). Use of 4D robust optimization could effectively reduce the sensitivity of the plan to interplay effects.

Three-dimensional robust optimization has become available in some commercial treatment planning systems, but 4D robust optimization is still new and is not available in most commercial planning systems at this time. For a given patient motion, a 3D robustly optimized plan is less sensitive to the interplay effect than a non−robustly optimized plan, and the 4D robustly optimized plan has the least interplay effect (53).

Motion mitigation for treatment delivery

Some patient and treatment parameters can be modified to minimize dose degradation caused by the interplay effect. Using larger spot sizes, lengthening the effective delivery time, and modifying the initial breathing phase when PT commences have all been shown to result in improved dose homogeneity in moving targets (15, 41, 48, 62-65). Notably, spot size is often facility dependent, although some institutions may have the same beam line with different spot sizes or different beams with different spot sizes (66). One of the practical methods of increasing spot size is the use of a range shifter with a larger air gap (67). More significantly, increasing the dose fractionation and using multiple beam angles result in greater improvements

in dose homogeneity (15, 18-20, 30, 41, 42, 51). However, the radiobiological effect with inhomogeneous fractionated doses has yet to be determined. Moreover, normal variations in breathing periods may result in less sensitivity to interplay effects (62). In addition to these factors, motion mitigation techniques for more robust delivery for moving targets have been or are being developed. The techniques described in the following sections should also be considered when motion is beyond the acceptable threshold.

Rescanning

Rescanning, also known as repainting (44), is a simple delivery-based technique used to minimize the dose uncertainty caused by the interplay effect. Rescanning allows dose inhomogeneities to be smoothed out or "smeared" by visiting each pencil-beam spot position several times during the delivery; however, it cannot reduce the dose blurring caused by the interplay effect (30). Rescanning techniques can be based on 2-dimensional (layered) or 3D (volumetric) rescanning, each of which has its own advantages and disadvantages (15, 20, 49-51, 68, 69). For layered rescanning, so-called isolayered rescanning has shown to be more practical and easier to implement (20, 49, 68). It involves setting the maximum dose or maximum MU for each visit of the spot locations. The maximum value per visit cannot be smaller than the minimum MU per dose, set by the hardware, which is machine dependent. Spots with weights that exceed the maximum are revisited after the previous scan until all rescanning is completed. The maximum dose or MU per visit could be reduced by increasing the number of rescannings, but this would also increase the treatment delivery time. In layered rescanning, each energy layer is completely rescanned before changing to the next energy layer. Volumetric rescanning consists of repetitive scanning through the whole target volume (49, 58) and thus requires systems with fast energy switching (49, 68). Recent evidence has suggested that volumetric scanning may suffer from coherence effects between the applied scan period and the period of motion, resulting in larger fluctuations in dose homogeneity (50, 51, 68, 69). For systems with fast energy switching times, both volumetric rescanning and layered rescanning could be viable approaches to motion mitigation (68). For systems with slower energy changes, layered rescanning is optimal (50, 68). Layered rescanning is currently in clinical use for some patients at several institutions. However, some delivery systems have inherent or mandatory rescanning requirements owing to system-specific parameters, and machine specifications may impose limitations on the implementation of any given rescanning strategy, whether layered or volumetric (51). Therefore, the effectiveness of rescanning should be evaluated on a facility-specific and patient-specific basis.

When an SFO technique is used, the number of fields used is equivalent to the number of volumetric rescannings, because each SFO field delivers a fraction of the prescribed dose to the entire target volume proportional to the field weight. Fractionated treatment can also provide effective rescanning (15, 19, 20, 41, 42). For hypofractionation treatments, rescanning should be mandated, either volumetric or layered, to reduce the uncertainty.

BH, gating, and tracking

BH, gating, and tracking are motion mitigation techniques that could minimize the effect of respiratory motion during delivery, thereby reducing potential underdosing of the target volume or excessive dose to healthy tissues for moving tumors (50). These techniques can be used in combination with layered or volumetric rescanning (50, 69). Notably, in-room volumetric imaging, such as CT on rails or cone beam CT (CBCT), is necessary for consistency in BH or gating level through monitoring the breathing baseline (fortunately, in-room volumetric imaging has become standard in new particle therapy facilities). For treatment delivery systems in which in-room volumetric imaging is not available, the use of implanted fiducial markers with fluoroscopic imaging could be an effective gating surrogate.

For BH treatment delivery, the radiation is delivered only when the patient is holding his or her breath to a certain level, and the beam is otherwise on hold. Active respiratory control and deep-inhalation BHs are already well-established motion mitigation strategies for photon delivery (70). For PBS-PT, a recent simulation study demonstrated that BH is a realistic clinical approach for treating thoracic tumors. However, large baseline shifts and small target volumes with substantial motion are potential concerns for BH treatment delivery (54), along with the ability of a patient to undergo BH in a consistent manner.

Gated treatment, on the other hand, involves radiation delivery that is synchronized with a gating signal and triggered only within a preset gating window. The gating signal can come from within the patient (eg, fiducials) or outside the patient (eg, via a real-time positioning management system). The correlation between gating signals and motion of the target volume should be established for each patient and monitored closely during each treatment session. The gating window is usually set at a certain percentage level of the averaged respiratory amplitude (ie, phase based). However, a fundamental assumption in gated treatment is that the respiratory signal correlates well with the actual tumor motion, which may not be the case for all patients. In addition, the primary tumor may move on a different trajectory from the nodes.

Currently, only a few centers are using gating systems for PBS-PT; one such system is in use at Hokkaido University (55, 71, 72). This "real-time imaging and gating system" involves implantation of gold fiducial markers near the tumor, which is used to identify marker positions relative to the tumor core. A 2-directional x-ray fluoroscopy system is then used to automatically pinpoint the marker positions on fluoroscopic images by pattern recognition, and those spatial positions are repeatedly calculated at regular intervals from 1 to 30 Hz. The treatment beam irradiates the targeted tumor only when the gold markers are within a few millimeters of the planned positions. The

high-speed nature of this system allows highly accurate irradiation of moving tumors. Compared with conventional methods that irradiate the entire area in which the tumor might migrate, this system can reduce the irradiated volume by 50% to 75%, which can represent a significant reduction in the irradiation of normal tissue (55, 56, 72, 73). Combining gating and rescanning, the National Institute of Radiological Sciences in Japan has implemented phase-controlled rescanning for its carbon ion system (74).

Tracking for particle therapy involves lateral adaptation of pencil-beam position and energy changes to modify the longitudinal position of the Bragg peak (58, 75). It also requires one to have a real-time 3D model of the patient to adapt for WET changes in the beam path. The concept of tracking was initially proposed for photon therapy with the use of multileaf collimators (76). Tracking for particle therapy is probably the most precise motion mitigation strategy, but it is technically challenging and is not available for clinical use at this time (39, 40, 58, 75, 77).

Quality Assurance and Adaptive Planning

Patient-specific quality assurance for PBS-PT, especially IMPT, is challenging because of the complex dose distributions of the treatment fields. Currently, measurements are made with a 2-dimensional ion chamber array detector for PBS treatment fields (78-80), and 3D detectors are being developed (81-84). To treat moving targets with a PBS technique, motion interplay effects and the effectiveness of motion mitigation strategies should be evaluated before patient treatment. A 4D phantom is recommended to be used for this purpose, as demonstrated in the literature (39, 40, 75). However, the challenge is the lack of any commercially available standardized 4D phantoms.

All patients should undergo repeat 4D CT verification simulations to determine whether adaptive replanning is needed to maintain target coverage (eg, >95% for the ICTV) and to avoid overdosing critical structures (4, 85). In the future, 4D magnetic resonance imaging could play an increasingly important role for motion verification with superior soft tissue contrast and no imaging dose (86, 87). Studies have suggested that even with robust optimization, about 30% of IMPT patients still require adaptive planning, mainly because of anatomy change over the course of the treatment (16, 88). In-room volumetric imaging techniques such as CBCT and in-room CT could also be used to identify possible anatomy changes. However, dose calculation on CBCT may not be sufficiently accurate, and 4D imaging also may not be available with these techniques. Therefore, verification 4D CT simulation for PBS-PT patients should be performed more frequently, such as on a weekly basis. The plan should be recalculated on the repeat 4D CT scans. Contours should be deformed from the planning CT scan to the verification CT scan, and the treating physician should review the new contours and dose-volume histograms. If an adaptive plan is deemed necessary, then it should be developed by using techniques as described earlier, and the same patient-specific quality assurance process should be repeated before treatment with the adapted plan. Interfractional changes in anatomy and motion patterns arising from tumor shrinkage or patient weight loss or gain further require systematic monitoring and timely adjustment of treatment plans over time (25). Adaptive PT has the ability to correct for dosimetric effects induced by interfractional anatomic changes and it complements the ability of image guided setup to correct for setup uncertainty.

Summary

We recommend the following strategies to successfully implement PBS-PT including IMPT for thoracic malignancies in clinical settings:

1. Perform basic measurements using a moving phantom to establish a threshold of the motion amplitude where the interplay effect is small.
2. Evaluate tumor motion using 4D CT—based evaluation and/or management to allow better selection of beam angles (as shown in Fig. E1; available online at www.redjournal.org).
3. Perform motion analysis. Compare 1FX4DDD and 1FX4DD to determine whether motion mitigation is necessary or sufficient.
4. Use dose distributions calculated on T0 and T50 to quantify the extremes of systematic dose degradation due to respiratory motion.
5. Use rescanning (either layered or volumetric) to reduce interplay effects, bearing in mind that use of SFO plans with multiple fields is effectively equivalent to volumetric rescanning and fractionated treatment delivery also provides effective rescanning. Use BH or gating as needed based on motion evaluation or a combination of any of these techniques with rescanning.
6. Use an optimized delivery sequence, including scanning direction, to minimize interplay effects.
7. Use 3D robust optimization to minimize the impact of organ motion. Use 4D robust optimization to further improve the robustness to intrafractional motion for large organ motion or in short fractionation schemes.
8. Perform verification 4D CT more frequently, such as on a weekly basis, to determine whether adaptive replanning is needed to maintain plan robustness.

Current challenges to implementing these recommendations are as follows:

1. Software tools for tumor motion analysis are not commercially available.
2. Commercial treatment planning systems do not calculate dynamic doses.

3. Four-dimensional robust optimization and 4D evaluation are not commercially available on many systems.
4. Rescanning and gating may not be available in some proton treatment delivery systems.
5. The capability to perform in-room volumetric imaging (CBCT, CT) has only recently become available at some institutions.
6. No standardized 4D phantom is commercially available for evaluation or accreditation.

We strongly encourage vendors to implement motion analysis tools, dynamic dose calculation, 4D robust optimization, rescanning, optimized delivery sequencing, gating, and diagnostic quality volumetric imaging and to commercialize a standard 4D phantom as quickly as possible. We recommend that each institution establish its acceptable tumor motion criteria based on its motion management strategy. If the extent of target motion is greater than the institutional criteria, then motion mitigation strategies such as rescanning, BH, or respiratory gating should be strongly considered. The availability of patient-specific, tumor motion—related dose uncertainty analysis and 3D and 4D robust optimization, as well as the availability of adaptive replanning to account for potential motion and anatomic changes during the course of radiation therapy, would further enhance the institution's ability to select proper patients. Each institution should follow the guidelines proposed here and optimize its motion management, planning, and delivery of PBS-PT using available tools and techniques. A learning curve is expected, and SFO plans should be considered first at the beginning of implementing PBS-PT to reduce motion uncertainty. If basic requirements cannot be met, patients should not be treated with PBS-PT. Enrollment in a clinical trial is strongly recommended.

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